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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/373,182 08/12/99 MCCLURE

K PC10240A

023913  
PFIZER INC  
235 E 42ND STREET  
NEW YORK NY 10017

HM12/0711

EXAMINER

WEBER, J

ART UNIT

PAPER NUMBER

1651

DATE MAILED:

07/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

# Office Action Summary

Application No.

09/373,182

Applicant(s)

MCCLURE ET AL.

Examiner

Jon P. Weber, Ph.D.

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-79 is/are pending in the application.
- 4a) Of the above claim(s) 1-59 and 62-79 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 60 and 61 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *Notice to Comply*.

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*Status of the Claims*

Claims 1-79 have been presented for examination.

*Election/Restrictions*

Applicant's election with traverse of Group V, claims 60-61, and the species 4-acetyl-3-methyl-1-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-piperazine-2-carboxylic acid hydroxamide, in Paper No. 7, filed 03 May 2001 is acknowledged. The traversal is on the ground(s) that there is no burden between Groups V-IX, claims 60-69, in particular and the remaining groups generally because the classes and subclasses to search and the relevant art are co-extensive. This is not found persuasive because: 1) the majority of the groups could not even be classified because the compositions being claimed are functionally defined or at best defined only by a class of functional group, hydroxamate; 2) each of the groups provides for compounds with distinctly different functional properties - it is highly unlikely that any given composition would meet the requirements of multiple and often contradictory functions; 3) each of the groups provides for concepts which must be separately searched in the patent as well as the non-patent literature. This poses a serious burden on the examination process. Claims 1-59 and 62-79 are withdrawn from consideration as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

*Specification*

The disclosure is objected to because of the following informalities:

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The communication filed 03 May 2001 is not fully responsive to the Office communication mailed 01 December 2000 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) for the response to this Office action to be complete. Additionally, the specification should be amended to reflect the SEQ ID NOs in the sequence listing.

The structure for the elected species at page 43, Table A, is missing a hydrogen on the hydroxamide.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosure provides no evidence of even a single compound which can meet the limitation of inhibiting TACE proteolysis of TNF- $\alpha$  without inhibiting MMP1. The best evidence

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is provided on Table A. Here the selectivity of compounds for TACE over MMP1 as given by the ratio of the IC50 values. These range from a low selectivity value of 42.4 to a high value of 558. The only disclosed compound exceeding selectivity of 500 is not even the elected species. Exhibiting selectivity is not equivalent to not inhibiting one while inhibiting the other.

Assuming that claims 60-61 should have been drawn to compounds which exhibit selectivity for TACE over MMP1, claims 60-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific compounds, does not reasonably provide enablement for any small molecule or hydroxamate which inhibits TACE catalyzed release of TNF- $\alpha$  from cell membranes at least 100-fold, preferably at least 500-fold more than it inhibits MMP1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

There are references which discuss hydroxamate-based inhibitors of TACE. There are references which discuss hydroxamate-based inhibitors of MMP1. However, it is rare for both enzymes to be considered with the same inhibitors in the same reference. Amour et al. (1998) discloses a number of hydroxamate-based inhibitors (Figure 2) which were tested against both MMP1 and TACE. The results summarized on Table 1 show that finding inhibitors that are highly selective for TACE over MMP1 does not appear to be trivial. Of the disclosed inhibitors, only BB-94 is a more selective inhibitor for TACE than MMP1, and then only by 2.8 fold. Andrews et al. (WO 9838179) also discloses hydroxamate-based inhibitors. On Table 3, it can be seen that compounds 7 and 8 appear to exhibit high selectivity for TACE over MMP1

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(Collagenase-1), TACE gets “+” and MMP1 gets “+++”, where these mean  $K_i < 1$  nM and 500 nM-1  $\mu$ M respectively suggesting at least 500 fold selectivity. Several other compounds exhibited intermediate selectivity “++” or 100-500 nM for  $K_i$ , corresponding to 100-500 fold selectivity. However, the table shows that most of the inhibitors do not exhibit selectivity. It would appear that even in these references (not prior art), evidence for inhibitors which are selective for TACE over MMP1 is difficult to obtain and not very predictable even by those who are very skilled in the art. That is, it is necessary but not sufficient to have an assay for the inhibition of each of the enzymes separately to obtain inhibitors which exhibit high selectivity for TACE over MMP1. Such inhibitors are only obtained on a case-by-case trial and error basis. The instant disclosure does not provide any teachings which would lead an ordinary artisan to believe that a general structure whose compounds mostly exhibit such selectivity has been disclosed. As discussed above the selectivity shown on Table A of the instant disclosure ranges from 46 to just over 500. Accordingly, the implied claims are not commensurate in scope with the enabling disclosure.

Other references cited by examiner but not relied upon are cited to establish the state of the art.

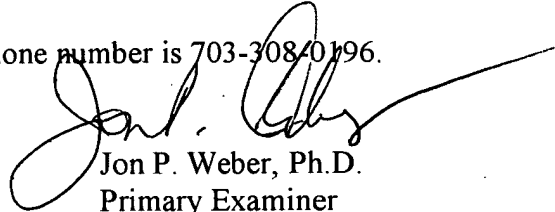
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P. Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-4743. The fax phone numbers for the

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organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jon P. Weber, Ph.D.  
Primary Examiner  
Art Unit 1651

JPW  
July 9, 2001